REMARKS/ARGUMENTS

Applicants acknowledge with appreciation the withdrawals of the rejections of claims and objection to the specification as detailed in the Office Action (October 21, 2004, page 2). Claims 1-3, 5-12, and 14-20 are pending in the application. Claim 12 has been cancelled. Applicants believe that the previously pending claims are fully supported by the specification as filed and meet the requirements of patentability; however, solely in order to advance prosecution, Applicants have amended the claims as detailed herein. Applicants expressly reserve the right to file continuing applications or take such other appropriate measures deemed necessary to protect the inventions described in the application as originally filed.

Claims 1, 3, 8, and 10 have been amended. Support for the amendments can be found in the original claims as well as in the specification, particularly on page 3, lines 17-20; page 7, lines 25-29; in Figure 1A and 1B; and on page 18 and in Table 1. The amended claims emphasize the importance to the invention that the nucleotide sequence of the claims encodes an engineered VSPβ protein comprising an amino acid sequence which differs from the amino acid sequence of a native protein, wherein said engineered protein has an altered amino acid composition in comparison to said native protein, wherein said altered amino acid composition comprises an increase in essential amino acid content to at least 5% to 10% of the amino acid content of said engineered protein, and wherein said engineered protein binds to at least one antibody, monoclonal antibody, or antibody fragment which binds to said native protein, wherein said native protein is VSPβ as set forth in SEQ ID NO:1.

In addition, claim 3 has been amended to clarify that the word "is" should not appear in the claim. This change had been previously made in the amendment filed August 14, 2003, and resubmitted at the Examiner's request on December 18, 2003; however, Applicants' representative overlooked the change in preparing the amended claim set in subsequent papers and has again marked the change in claim 3 submitted herewith simply to correct those later errors; if this particular change is superfluous or unnecessary, it is respectfully requested that the Examiner disregard it.

No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Rejection of Claims Under 35 U.S.C.§112, First Paragraph, Should Be Withdrawn

The Office Action (dated October 21, 2004, page 4) has rejected claims 1-3, 5-12, and 14-20 under 35 U.S.C. §112, first paragraph, as "failing to comply with the written description requirement" and as lacking enablement for the breadth of the claims (Office Action dated October 21, 2004, page 6 *et seq.*). Claim 12 has been cancelled. Independent claims 1 and 8 (and therefore also claims 2-7, which are dependent on or incorporate the limitations of claim 1, as well as claims 9-11 and 14-20, which are dependent on or incorporate the limitations of claim 8) have been amended to specify that the nucleotide sequence of the claims encodes an engineered VSPβ protein comprising an amino acid sequence which differs from the amino acid sequence of a native protein, wherein said engineered protein has an altered amino acid composition in comparison to said native protein, wherein said altered amino acid composition comprises an increase in essential amino acid content to at least 5% to 10% of the amino acid content of said engineered protein, and wherein said engineered protein binds to at least one antibody, monoclonal antibody, or antibody fragment which binds to said native protein, wherein said native protein is VSPβ as set forth in SEQ ID NO:1.

The Examiner kindly conducted an interview regarding the claims in this case by telephone on August 17, 2004, during which the Examiner discussed his belief that the identity of the sequences referred to in the claims was unclear and that the examples provided in the specification were insufficient to support the breadth of the claims then pending. While Applicants respectfully disagree with this assessment, solely in order to advance prosecution, the claims have been amended as indicated above. Applicants further note that dependent claims 3 and 10 have been amended to require an increase in the content of an essential amino acid which is methionine, leucine, isoleucine, or valine, which are essential amino acids as defined in the specification and which also share particular properties such that the substitution of one of the members of this group for another member of this group is generally considered in the art to be a conservative change (see, *e.g.*, specification page 3, lines 27-30, discussing essential amino acids; the discussion of engineering VSPβ for increased methionine on page 16 *et seq.*,

particularly on page 18; and the information regarding various substitutions shown in Table 1 on pages 22 and 23).

While the written description and enablement rejections made in the Office Action have not been raised against the claims as amended herein, the rejections will be addressed in so far as they may apply to the newly amended claims. The Office Action (October 21, 2004, page 4 *et seq.*) states that:

> Applicants fail to describe a representative number of VSPα or VSPβ proteins having an altered amino acid composition comprising an increase in the essential amino acid composition of any number of essential amino acids to at least 5% that binds to at least one antibody, monoclonal antibody, antibody fragment, or protein which also binds to the native form of VSPα or VSPβ. Applicants only describe VSPβ10 (SEQ ID NO:8) limited to alterations of specific amino acid positions in VSPβ from soybean. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of nucleic acid sequence....

Applicants respectfully disagree with this conclusion with regard to the claims as previously pending, and also disagree with this conclusion with regard to the claims as amended herein. The present specification identifies the known amino acid sequences of VSPβ in Figure 1 and the Figure 1 legend on page 3, line 1 *et seq.*, as well as the sequences of several methionine-enriched VSPβ variants and a nucleic acid molecule encoding an engineered protein (VSPβ-Met 10; Figure 4).

Moreover, as previously acknowledged in the Office Action of June 17, 2003 (page 4):

> Applicant teaches proposed methionine enriched VSPβ variants based on conserved amino acid residues within VSP homologues (pages 15-16 and Figure 2); positions of possible tolerated amino acid substitutions within VSPβ (pages 16-19); a strategy for isolating correctly folded methionine enriched variants of VSPβ by testing for binding to a VSPβ specific antibody (pages 19-22) and methionine enriched variant VSPβ-[Met]10 binding to wild type VSPβ specific antibodies (page 19).

However, the Office Action (October 21, 2004, page 5) concludes that Applicants did not "meet either prong of the two-prong test set forth by *Eli Lilly*" because "Applicants [failed] to describe a representative number of VSPα or VSPβ proteins" meeting the limitations of the claims and because "Applicants fail to describe structural features common to members of the

claimed genus." Applicants respectfully disagree. Applicants note that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. *See,* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, First Paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2001). Applicants respectfully emphasize that the knowledge and level of skill in the art would allow a person of ordinary skill to envision the claimed invention.

Furthermore, the description of a claimed genus can be by structure, formula, chemical name, or physical properties. *See, Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), citing *Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). A genus of nucleotide sequences such as those recited in independent claims 1 and 8 may therefore be described by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *See, Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* 66 Fed. Reg. 1099, 1106 (2001). The recitations that the native protein is VSPβ as set forth in SEQ ID NO:1 and that the engineered protein binds to at least one antibody, monoclonal antibody, or antibody fragment which binds to said native protein is sufficient to satisfy the written description requirement.

Applicants respectfully submit that the nucleotide sequences encompassed by genus claims 1 and 8 are defined by relevant identifying physical and chemical properties. In fact, the common attributes or features of the elements possessed by the members of these genera is that they encode an engineered VSPβ protein which comprises an amino acid sequence that is defined in reference to SEQ ID NO:1 and which bind to at least one antibody, monoclonal antibody, or antibody fragment which binds to the native VSPβ. The necessary common features of the claimed genus are clear.

Applicants further note that the Federal Circuit has explicitly stated that

> *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003). *See also, Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320 (noting that "[i]n more recent cases, however, this court has distinguished *Lilly*" and further noting that in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002), "neither the specification nor the deposited biological material recited the precise 'structure, formula, chemical name, or physical properties' required by *Lilly*.")

In summary, the description of a representative number of species *does not* require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicants submit that the relevant identifying physical and chemical properties of the disclosed genus would be clearly recognized by one of skill in the art and consequently, Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Accordingly, the rejection of claims 1-3, 5-11, and 14-20 under 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn.

The Office Action (October 21, 2004, page 6 *et seq.*) maintained the rejection of claims 1-3, 5-12, and 14-20 as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. While this enablement rejection has not been raised against the claims as amended herein, the rejection will be addressed in so far as it may apply to the newly amended claims.

The present specification discloses the sequences of several methionine-enriched VSPβ variants and a nucleic acid molecule encoding an engineered protein (VSPβ-Met 10; see Figure 4). As noted in a previous Office Action (6/17/03, page 4):

> Applicant teaches proposed methionine enriched VSPβ variants based on conserved amino acid residues within VSP homologues (pages 15-16 and Figure 2); positions of possible tolerated amino acid substitutions within

> VSPβ (pages 16-19); a strategy for isolating correctly folded methionine enriched variants of VSPβ by testing for binding to a VSPβ specific antibody (pages 19-22) and methionine enriched variant VSPβ-[Met]10 binding to wild type VSPβ specific antibodies (page 19).

Thus, the present specification provides exemplary nucleotide and amino acid sequences as well as guidance regarding evaluation of the functional limitations of the claims. Applicants believe that the teachings of the present specification, when considered by those of skill in the art, satisfy the enablement requirement.

In order to advance prosecution, claims 1 and 8 have been amended to specify that the nucleotide sequence of the claims encodes an engineered VSPβ protein comprising an amino acid sequence which differs from the amino acid sequence of a native protein, wherein said engineered protein has an altered amino acid composition in comparison to said native protein, wherein said altered amino acid composition comprises an increase in essential amino acid content to at least 5% to 10% of the amino acid content of said engineered protein, and wherein said engineered protein binds to at least one antibody, monoclonal antibody, or antibody fragment which binds to said native protein, wherein said native protein is VSPβ as set forth in SEQ ID NO:1. As discussed previously during prosecution, it is expected that the engineered VSPβ proteins of the claims will retain the conformation of the native VSPβ protein as determined by their ability to bind to at least one antibody, monoclonal antibody, or antibody fragment. As illustrated by the guidance and examples provided in the specification, the amount of experimentation required to make and use the claimed invention would not be considered undue by one of skill in the art. Particularly, Applicants have provided an exemplary sequences of VSPβ as well as exemplary sequences of "VSPβ-Met10," "VSPβ-Met20," and "VSPβ-Met30" (see, *e.g.*, the sequence listing). Applicants have provided extensive guidance for making proteins having altered amino acid compositions, for example, on pages 5-7 (guidance for making substitutions and discussing changes in essential amino acid content) and in the Experimental section on pages 13 *et seq*. Particularly, pages 13 and 16-17 include an extensive discussion of various protein modification strategies and describe positions expected to tolerate conservative and non-conservative substitutions; see also the data provided in Tables 1 and 2 on pages 22 and 23. The specification provides a working example (on page 19) in which VSPβ-

Met10 was produced in *E.coli* and found to bind to the same antibodies as wild-type VSPβ. Applicants believe that this amount of guidance is sufficient for one of skill in the art to make and use the claimed invention.

Applicants stress that when evaluating the quantity of experimentation required, the court looks to the amount of experimentation required to practice a single embodiment of the invention rather than the amount required to practice every embodiment of the invention. For example, in *In re Wands* (858 F.2d 731 (Fed. Cir. 1988)), the claims at issue were drawn to immunoassay methods using any monoclonal antibody having a binding affinity for HbsAg of at least 10^{-9} M. The PTO had taken the position that the claim was not enabled, as it would take undue experimentation to make the monoclonal antibodies required for the assay. The Federal Circuit reversed and held that the claims were enabled because the amount of experimentation required to isolate monoclonal antibodies and screen for those having the correct affinity was not undue. *Id.* Clearly, the Federal Circuit did not contemplate that every antibody useful in the methods of the claim must be identified. Rather, the court considered the amount of experimentation required to identify one or a few monoclonal antibodies having the required affinity. *See also, Johns Hopkins University v. Cellpro*, 931 F. Supp. 303, 324 (D. Del. 1996), *aff'd in part, vacated in part, and remanded*, 47 USPQ2d 1705 (Fed. Cir. 1998) (stating that "[t]he specification need only enable one mode of making the claimed invention.").

In the instant case, the quantity of experimentation required to practice the invention amounts to only a few steps: generating a nucleic acid molecule comprising a nucleotide sequence that encodes protein having an altered amino acid composition and determining whether that protein binds to at least one antibody which binds to the native VSPβ protein as set forth in SEQ ID NO:1. All of these steps are readily within the skill of those in the art and such assays, while routine in the art, have further been presented in the specification, particularly in the working example described on page 19. Some of the claims (*e.g.*, claim 8 and claims dependent thereon) are drawn to plants containing nucleotide sequences encoding such proteins, and the additional steps required to practice these claims are also routinely performed by those of skill in the art.

The Office Action correctly alludes to the fact that some of the nucleotide sequences that encode proteins meeting the amino acid content limitation of the claims might not encode proteins that meet the antibody (or antibody-fragment)-binding limitation of the claims (see, *e.g.*, Office Action of October 21, 2004, page 8, second full paragraph). However, Applicants note that the existence of inoperative embodiments within the scope of the claims does not render the claims invalid. *See, Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984) (noting that one of skill in the art would be able to determine which embodiments were operative). Further, even in an unpredictable art, enablement does not require "disclosure of a test of every species covered by a claim." *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976) (noting that such a requirement would "force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments.")

As discussed above, ample guidance is provided to allow one of skill in the art to make and use the claimed invention. Consequently, contrary to the conclusions stated in the Office Action, the quantity of experimentation necessary and the amount of guidance presented in the specification is sufficient to enable the claimed nucleic acid molecules and plants. Accordingly, the rejection of the claims under 35 U.S.C. §112, first paragraph, for lacking enablement should be withdrawn.

In view of the above arguments and amendments, Applicants believe that all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been overcome. Accordingly, it is respectfully submitted that the rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

The Rejection of Claims under 35 U.S.C. §103 Should Be Withdrawn

The Office Action (October 21, 2004, page 9) rejected claims 1-3, 5-12, and 14-20 under 35 U.S.C. §103(a) over Staswick *et al.* (1990) *The Plant Cell* 2: 1-6 in view of Dyer *et al.* (1995) *J. Prot. Chem.* 14: 665-678. Applicants respectfully disagree with this conclusion.

Applicants reiterate that in order to advance prosecution, claims 1 and 8 have been amended to specify that the nucleotide sequence of the claims encodes an engineered VSPβ protein comprising an amino acid sequence which differs from the amino acid sequence of a

native protein, wherein said engineered protein has an altered amino acid composition in comparison to said native protein, wherein said altered amino acid composition comprises an increase in essential amino acid content to at least 5% to 10% of the amino acid content of said engineered protein, and wherein said engineered protein binds to at least one antibody, monoclonal antibody, or antibody fragment which binds to said native protein, wherein said native protein is VSPβ as set forth in SEQ ID NO:1 (also referred to herein as the "binding limitation").

The Office Action characterizes the Staswick reference as follows (Office Action of October 21, 2004, page 10):

> Staswick teaches that VSPα and VSPβ cDNA and protein sequences from soybean are known in the art; that VSP antisera cross react with specific leaf proteins in several leguminous species (page 4, column 2 3rd paragraph); and teaches that VSP subunits bind to each other as a dimer (page 1 column 2 lines 7-11); and suggests engineering VSPα and VSPβ protein sequences from soybean to increase the availability of nitrogen and sulfur precursors for seed protein synthesis in transgenic plants....

The Office Action characterizes the Dyer reference, in part, as follows (Office Action of October 21, 2004, page 10):

> Dyer teaches increasing essential amino acid content by substitution of the essential amino acid methionine for genetically variant hydrophobic residues in the β-barrels and loop structures of phaseolin, a seed storage protein from the common bean, wherein the protein maintains its' structural integrity....

The Office Action concludes (Office Action of October 21, 2004, page 11):

> It would have been obvious to modify the invention of Staswick by substituting the essential amino acid methionine for hydrophobic residues as taught by Dyer to increase the essential amino acid content or methionine content of VSPα and VSPβ from soybean to at least 5%, 10%, or 20%. One of skill in the art would have been motivated by the teachings of Staswick...that the VSPβ and VSPα protein could be isolated and antisera comprising antibodies raised against VSPβ and VSPα would bind to other plant vegetative proteins....

Applicants note that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest

all the claim limitations. Second, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to produce the claimed invention. Finally, there must be a reasonable expectation of success (see MPEP §2142).

While Dyer does teach an increase in the essential amino acid content of a protein, Applicants note that Dyer *et al.* actually teaches away from the use of methods to assess the structure of a protein where those methods are not based on "[t]hree-dimensional structural information based on X-ray crystallographic analysis." Dyer *et al.* state (page 667, column I): "efforts toward protein engineering of seed storage proteins ***have been frustrated primarily by lack of accurate structural information*** of the target proteins ***and by the inability to characterize structural alterations*** brought about by the introduced mutations" (emphasis added). Applicants also note that the Dyer *et al.* study was published in 1995, long after antibodies, monoclonal antibodies, and antibody fragments and their uses were well known in the art.

The Office Action concludes that the combination of the teachings of Dyer *et al.* and Staswick *et al.* would have been obvious to one of ordinary skill in the art and that one would have been motivated to practice such methods. However, this conclusion flatly contradicts the insistence of Dyer *et al.* that X-ray crystallographic structural information was essential to progress and that protein engineering had been frustrated in the absence of such information. Thus, Dyer *et al.*, who must be considered those of skill in the art, ***taught away*** from the use of methods that did not depend on X-ray crystallographic structural information. Moreover, there is no suggestion whatsoever in Staswick *et al.* that antisera specific to a particular protein could be used to confirm the structure of a modified protein. Applicants emphasize that in contrast to the teachings of Dyer *et al.*, the present invention provides the benefit that structural information is ***not*** required to make and use an altered protein.

Thus, neither Staswick *et al.* nor Dyer *et al.* nor the combination thereof teaches or suggests the claimed invention which is a nucleotide sequence encoding an engineered VSPβ protein having a particular amino acid composition wherein said engineered protein binds to at

least one antibody, monoclonal antibody, or antibody fragment which binds to a native protein which is VSPβ as set forth in SEQ ID NO:1.

Therefore, because the combination of Staswick *et al.* and Dyer *et al.* does not render the claims obvious, Applicants respectfully request reconsideration and withdrawal of this rejection of claims under 35 U.S.C. §103(a).

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§112, first paragraph, and 103(a) are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Leigh W. Thorne
Registration No. 47,992

Customer No. 29122
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

"Express Mail" mailing label number EV 387068846 US
Date of Deposit January 21, 2005

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Lynda-Jo Pixley

RTA2171882v1

Amendments to the Drawings:

Replacement drawings for Figures 1A and 1B are being submitted herewith. The shading found in the drawings as previously submitted has been removed and the letters (*i.e.*, amino acid designations) in the boxes that were previously shaded in the figure have been reformatted into a bold font. No new matter has been added by way of amendment, as the differences between the original figures and the replacement figures represent a mere change in format rather than any change in content. Applicants sincerely hope that the corrected drawing is acceptable; if it is not, Applicants respectfully request that any remaining issues with the drawing be stated with particularity so that appropriate correction may be made promptly.